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| EXAMINER | |
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| NOAKES, SUZANNE MARIE | |

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**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/582,277 | NIELSEN ET AL. | |
| | Examiner | Art Unit | |
| | SUZANNE M. NOAKES | 1656 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *03 June 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *27-46* is/are pending in the application.

4a) Of the above claim(s) *27-40 and 42-45* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *41 and 46* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *06/10/2006*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

**DETAILED ACTION**

***Election/Restrictions***

1. Applicant's election with traverse of Group II, claims 41 and 46, in the reply filed on 03 June 2008 is acknowledged. The traversal is on the ground(s) that according to 37 C.F.R. 1.475(b) an international or nation stage application complies with the unity of invention requirement if the claims are drawn only to one of the following combinantions or categories:

(1) A product and a process specially adapted for the manufacture of said product; or
(2) A product and a process of use of said product; or
(3) A product, a process specially adapted for the manufacture of the said product, and a use of the said product; or
(4) A process and an apparatus or means specifically designed for carrying out the said process; or
(5) A product, a process specially adapted for the manufacture of the said product, and an apparatus or means specifically designed for carrying out the said process.

Applicants further argue that the International Searching Authority did not find a lack of unity of invention.

This is not found persuasive because according to 37 C.F.R. 1.475 part II: "***If***, *however, an independent claim does not avoid the prior art*, then the question whether there is still an inventive link between all the claims dependent on that claim needs to be carefully considered. If there is no link remaining, an objection of lack of unity a posteriori (that is, arising only after assessment of the prior art) may be raised." (see

MPEP 1850, and 37 C.F.R. 1.475 II). In the instant case, the independent claim does not avoid the prior art and thus the unity of invention linking the claims, even dependent claims, is lost. With regard to the ISA findings regarding the unity of invention, it is specifically noted that the ISA were searching a completely different set of claims (e.g. Applicants cancelled all claims searched by the ISA and presented new claims in the National Stage application).

The requirement is still deemed proper and is therefore made FINAL.

***Status of the Claims***

2. Claims 27-46 are pending. Claims 27-40 and 42-45 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected subject matter, there being no allowable generic or linking claim. Claims 41 and 46 are subject to Examination on the merits.

***Information Disclosure Statement***

3. The information disclosure statement (IDS) submitted on 10 June 2006 has been considered by the examiner. See initialed and signed PTO-1449.

***Claim Objections***

4. Claims 41 and 46 are objected to because of the following informalities:

A. Said claims are dependent upon withdrawn, non-elected claims.

B. In the first instance where an acronym is used, said acronym should be spelled out in full, followed by the abbreviation in parenthesis. Thus, in claim 41, "MrgA" should be spelled out as 'metallo regulated gene A (MrgA)' as recited in the specification, p. 1, line 13.

Appropriate corrections are required.

***Claim Rejections - 35 USC § 112 – 1st paragraph***

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claim 41 is rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of making/enhancing the secretion of a protein of interest by cultivating cells from the genus of *Bacillus* wherein a progeny cell is derived from a parent cell and wherein said progeny cell encodes at least an MrgA protein and wherein said cells are derived from (and cultivated) the genus *Bacillus*, does not reasonably provide enablement for methods of making or enhancing the secretion of a protein of interest by cultivating cells expressing MrgA wherein said protein is expressed in any kind of cells. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

In the instant case, the claims are drawn to a method of enhancing the secretion of a protein or interesting by expressing said protein in a progeny cell derived from a

parent cell wherein: the progeny cell comprises at least one MrgA protein or functional homologue thereof which is operably linked to a DNA segment; b) said progeny cell contains two or more copies of a MrgA gene or functional homologue thereof; or c) the progeny cell is somehow mutated with respect to the parent cell. However, it is noted that MrgA is a metallo regulated gene that is expressed only in cells of the genus of *Bacillus*. Thus, expressing said protein in a completely unrelated host cell which operates and secretes proteins utilizing entirely different secretion pathways, genes, proteins etc. would not be expected to have any impact or function upon other cells secretion of proteins and thus no enhancement would be expected to occur. For instance, *E. coli* requires the presence of SecA and SecB proteins but has no MrgA protein or analogue thereof used in the protein secretion pathway (see p. 2579, 1st column, 2nd paragraph of van Wely et al., 2000, cited on IDS). While it would be possible to make a protein of interest using cells having more MrgA being expressed as well as the protein of interest (as in claim 46) the protein of interest would not be expected to be produced in greater amounts if the parent/progeny cells are anything other than from the genus *Bacillus*. (It is noted that claim 46 does not require an enhancement or increase in the production of the protein of interest and thus is not included in this rejection).

The factors to be considered in determining whether undue experimentation is required are summarized In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988). The court in Wands states: "Enablement is not precluded by the necessity for some experimentation such as routine screening. However, experimentation needed to

practice the invention must not be undue experimentation. The key word is 'undue,' not 'experimentation.' " (Wands, 8 USPQ2d 1404). Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation required to make or use the invention. "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations." (Wands, 8 USPQ2d 1404). The factors to be considered in determining whether undue experimentation is required include: (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

N.B. MPEP 2164.04 states, "[w]hile the analysis and conclusion of a lack of enablement are based on the factors discussed in MPEP § 2164.01(a) and the evidence as a whole, it is not necessary to discuss each factor in the written enablement rejection" and that "[t]he language should focus on those factors, reasons, and evidence that lead the examiner to conclude that the specification fails to teach how to make and use the claimed invention without undue experimentation, or that the scope of any enablement provided to one skilled in the art is not commensurate with the scope of protection sought by the claims." Accordingly, the Factors most relevant to the instant rejection are addressed in detail below.

In the instant case there is a considerable expectation that undue experimentation would imposed upon a skilled artisan because, as noted above, the

secretion 'machinery' of proteins and enzymes is not maintained across all kinds of cells. *E. coli* is dependent upon several different pathways such as SEC or the twin arginine translocation pathways, yet does not require or use an MrgA homologue. Thus, eukaryotes use many more different pathways as said organisms have additional organelles and sites of protein production (e.g. Endoplasmic reticulum, Golgi apparatus, etc. - see Sakaguchi, Curr. Op. Biotech. 1997, 8:595-601). While prokaryotes generally have several different general secretory pathways such as SEC or TAT (see Pugsley et al. Mol. Micro, 2003, 52(1):3-11) there are several specific protein secretion pathways known (see Puglsley, p. 6, Autotransporters) since one is not apprised to which secretory pathway MrgA is involved in as the prior art does not acknowledge said proteins assistance with protein secretion and the specification is silent to this then unless the pathway which uses MrgA is also present in other host cells, one skilled in the art would have no idea which host parent cells/progeny cells would function to enhance secretion. The predictability of which host cells will utilize MrgA is completely unknown and thus the quantity of experimentation would be expected to vast because the only working Examples in the specification utilize only *Bacillus* host cells.

Therefore, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

7. Claims 41 and 46 are under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for methods of enhancing the secretion or a protein

or interest as well as methods of isolating said protein of interest by utilizing progeny cells which express the MrgA protein of SEQ ID NO:2, does not reasonably provide enablement for the same methods utilizing progeny cells expressing functional homologues of MrgA, and/or any or all DNA segments linked to said homologues; or progeny cells that have been "mutated with respect to the parent cell" and which said progeny cell produces more MrgA protein than the parent cell.

The factors to be considered in determining whether undue experimentation is required are summarized above.

In the instant case the invention hinges on the findings by Applicants that MrgA is involved in protein secretion, at least in the genus *Bacillus*. Said protein is a 153 amino acid protein, believed to be involved in oxidative stress among other things such as DNA binding and metal binding (see specification, p. 1, Background and see sequence listing, SEQ ID NO: 2). According to Chen et al. (1995, cited on IDS), the 153 amino acid protein has a molecular mass of about 17.3 kDa (see p. 296, 1st column, 1st line). However, said protein is known to form into an oligormeric complex (see p. 297, 2nd column, 2nd paragraph). However, exactly how many monomers form the active complex is not known. Post-filing evidence, however, suggests that MrgA forms a dodecamer as determined by the protein crystal structure of Essen et al. (2007, deposited as 2chp in the Protein Data Bank). Yet, no other structural detail or biochemical details of this proteins vital amino acids, and thus the nucleotides of the gene encoding said protein, are known in the prior art.

Applicants define a "functional homologue" of a MrgA protein as one which has as low as 50% sequence identity with a wild-type MrgA protein (see specification, p. 14, 1st paragraph). However, there is no information in the specification or the prior art to detail to one skilled in the art what mutations are acceptable in the MrgA protein of SEQ ID NO: 2 which would also result in a functional protein that would be able to assist in heterologous or homologous protein secretions. Thus, it is asserted that the scope of patent protection sought by Applicant as defined by the claims fails to correlate reasonably with the scope of enabling disclosure set forth in the specification for the following reasons.

The problem of prediction protein structure from sequence data and in turn utilizing predicted structural determinations to ascertain functional aspects of the protein is extremely complex. While it is known that many amino acid substitutions are generally possible in any given protein, the positions within the protein's sequence where such amino acid substitutions can be made with a reasonable expectation of success is limited. In the instant case, the MrgA protein forms a complex of 12 monomers, however, which amino acids are crucial for said complexes formation is not disclosed in the specification nor in the prior art (note, the 3-D crystal structure was filed/deposited after the instant application). It is well known that certain positions in the sequence are critical to the protein's structure/function relationship, such as various sites or regions directly involved in binding, activity and in providing the correct three-dimensional spatial orientation of binding and active sites. These regions can tolerate only relatively conservative substitutions *or* no substitutions as all (see Bowie et al. pp.

1306-10, specifically p. 1306 column 2, paragraph 2; Wells pp. 8509-8517). However, Applicant has provided little or no guidance beyond the mere presentation of sequence data to enable one of ordinary skill in the art to determine, without undue experimentation, the positions in the protein which are tolerant to change (e.g. by amino acid substitutions or deletions or insertions), and the nature and extent of changes that can be made in these positions which would result in a gene which encoded a functional MrgA protein and still was able to assist in protein secretion as well as in recovering various proteins of interest. Although the specification outlines art-recognized procedures for producing and screening for active protein variants (see p. 15 of instant specification), this is not adequate guidance as to the nature of active derivatives that may be constructed, but is merely an invitation to the artisan to use the current invention as a starting point for further experimentation. Even if an active or binding site were identified in the specification, they may not be sufficient, as the ordinary artisan would immediately recognize that an active or binding site must assume the proper three-dimensional configuration to be active, which conformation is dependent upon the surrounding residues and thus little to no MrgA protein would likely result (or at the minimum inclusion bodies); therefore substitution of non-essential residues can often destroy activity or would inhibit secretion of even the MrgA protein itself let alone the proteins of interest.

Finally, there is no mention outside that made in the claims, wherein "the progeny cell is mutated with respect to the parent cell". This could encompass exposing the cells to radiation, chemical treatments, site-directed mutagenesis, etc. However,

how or what is being mutated is not defined and encompasses an enormous amount of techniques which can result in "mutated cells", however, there is no guidance as to which ones might even begin to result in cells that produce more MrgA protein than the previous, other than the ones encompasses by parts a) and b) (noted in claim 27).

Due to the large quantity of experimentation necessary to generate the infinite number of derivatives recited in the claims and screen the same for activity, the lack of direction/guidance presented in the specification regarding which structural features are required in order to provide activity, the absence of working examples directed to the same, the complex nature of the invention, the state of the prior art which established the unpredictability of the effects of mutation on protein structure and function, and the breadth of the claims which fail to recite any structural or functional limitations, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

*Written Description:*

8. Claims 41 and 46 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The MPEP states that the purpose of the written description requirement is to ensure that the inventor had possession, at the time the invention was made, of the specific subject matter claimed. The courts have stated:

> "To fulfill the written description requirement, a patent specification must describe an invention and do so in sufficient detail that one skilled in the art can clearly conclude that "the inventor invented the claimed invention." *Lockwood v. American Airlines, Inc.*, 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (Fed. Cir. 1997); *In re Gostelli*, 872 F.2d 1008, 1012, 10 USPQ2d 1614, 1618 (Fed. Cir. 1989) ("[T]he description must clearly allow persons of ordinary skill in the art to recognize that [the inventor] invented what is claimed."). Thus, an applicant complies with the written description requirement "by describing the invention, with all its claimed limitations, not that which makes it obvious," and by using "such descriptive means as words, structures, figures, diagrams, formulas, etc., that set forth the claimed invention." *Lockwood*, 107 F.3d at 1572, 41 USPQ2d at 1966." *Regents of the University of California v. Eli Lilly & Co.*, 43 USPQ2d 1398.

Further, for a broad generic claim, the specification must provide adequate written description to identify the genus of the claim. In *Regents of the University of California v. Eli Lilly & Co.* the court stated:

> "A written description of an invention involving a chemical genus, like a description of a chemical species, 'requires a precise definition, such as by structure, formula, [or] chemical name,' of the claimed subject matter sufficient to distinguish it from other materials." *Fiers*, 984 F.2d at 1171, 25 USPQ2d 1601; *In re Smythe*, 480 F.2d 1376, 1383, 178 USPQ 279, 284985 (CCPA 1973) ("In other cases, particularly but not necessarily, chemical cases, where there is unpredictability in performance of certain species or subcombinations other than those specifically enumerated, one skilled in the art may be found not to have been placed in possession of a genus ...") *Regents of the University of California v. Eli Lilly & Co.*, 43 USPQ2d 1398.

MPEP § 2163 further states that if a biomolecule is described only by a functional characteristic, without any disclosed correlation between function and structure of the sequence, it is "not sufficient characteristic for written description purposes, even when accompanied by a method of obtaining the claimed sequence." MPEP § 2163 does state that for a generic claim the genus can be adequately described if the disclosure presents a sufficient number of representative species that encompass the genus. If the genus has a substantial variance, the disclosure must describe a sufficient variety of

species to reflect the variation within that genus. See MPEP § 2163. Although the MPEP does not define what constitute a sufficient number of representative species, the courts have indicated what do not constitute a representative number of species to adequately describe a broad generic. In *Gostelli*, the courts determined that the disclosure of two chemical compounds within a subgenus did not describe that subgenus. *In re Gostelli*, 872, F.2d at 1012, 10 USPQ2d at 1618.

In the instant case, as noted above, the claims are drawn to methods of enhancing secretion of proteins of interest or recovering proteins of interest by using progeny cells that express a MrgA protein, MrgA functional homologues, or have progeny cells mutated with respect to the parent cell. However, the specification notes that a MrgA functional homologue can be any protein that that has at least 50% or more sequence identity with an MrgA protein (see specification, p. 15, 1st paragraph). However, which MrgA protein is not known, e.g. it does not have to be wild-type/SEQ ID NO: 2, it could already be a derivative, mutant or variant MrgA protein. Thus, given the broad but reasonable interpretation of the claims as well as the definitions outlined in the specification, the claims are drawn to a huge genus of MrgA polypeptides which have no structure-function correlation; in addition, the variance in this genus of polypeptides is represented in the specification by a single species, which is not considered sufficient as said species is no representative of the entire variable genus of MrgA polypeptides. Furthermore, the invention hinges on producing functional MrgA, however, nowhere is it disclosed which amino acids are vital to the proteins own secretion and how the protein's activity is involved with secreting other proteins (other

than requiring an active protein). It is noted that the Court has held that the disclosure of screening assays and general classes of compounds was not adequate to describe compounds having the desired activity: without disclosure of which peptides, polynucleotides, or small organic molecules have the desired characteristic, the claims failed to meet the description requirement of § 112. See *University of Rochester v. G.D. Searle & Co., Inc.*, 69 USPQ2d 1886,1895 (Fed. Cir. 2004).

Thus, it is expected that a skilled artisan cannot, as one can do with a fully described genus, visualize or recognize the identity of the members of the genus that exhibit this functional property.

***Claim Rejections - 35 USC § 102***

9. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

10. Claims 14 and 46 are rejected under 35 U.S.C. 102(b) as being anticipated by Chen et al. (Mol. Micro., 1995, cited on IDS).

Chen et al. teach a strain of parent cells known as MA991 which are hydrogen peroxide sensitive cells that constitutively express catalase (KatA) and alkyl hydrogen peroxide reductases (AhpC and AhpF), as well as two other proteins of 113 kDa and 1kDa and transformed these cells by inserting the genes *mrgA-lacZ* to express said proteins, thus resulting in progeny cells (strain HB1032) – See p. 297, 1st column,

paragraphs 1-2. It was noted that N-terminal sequencing indicated that the 116 kDa protein over expressed in MA991 was identical to MrgA, which was later confirmed (See p. 297, 1st column, paragraph 2). Thus, strain HB1032 was expressing at least two copies of MrgA (e.g. one naturally occurring in the parent strain, the other having been introduced into the progeny cell) and thus, the progeny cell produces greater amounts of MrgA; It is asserted that these cells thus anticipate a, b, and c of the progeny cell (see claim 27) and that inherently the secretion of the proteins of interest, e.g. KatA, AhpC, AhpF and/or MrgA itself, must necessarily have been enhanced. Finally, there is no requirement in the claims that the protein of interest itself can not be the protein of interest. It is noted that the MrgA fusion proteins overexpressed in the HB1032 strain was purified to homogeneity (see p. 299, 2nd column, 1st two paragraphs).

***Conclusion***

11. No claim is allowed.

12. Any inquiry concerning this communication or earlier communications from the examiner should be directed to SUZANNE M. NOAKES whose telephone number is (571)272-2924. The examiner can normally be reached on 7.00 AM-3.30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Kathleen Kerr Bragdon can be reached on 571-272-0931. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Suzanne M. Noakes/
Examiner, Art Unit 1656
09 September 2008